Short Communication

Dietary Intake of Heterocyclic Amines and Benzo(*a*)Pyrene: Associations with Pancreatic Cancer

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Abstract

Objective: **Heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons, formed in temperature- and time-dependent manners during the cooking of meat, are mutagens and carcinogens. We sought to assess the association between dietary intake of HCA and benzo(*a*)pyrene [B(*a*)P] and exocrine pancreatic cancer in a population-based case-control study.**
Methods: **Subjects (193 cases and 674 controls) provided information on their usual meat intake and preparation method, e.g., stewed, fried, or grilled/barbecued, etc. Meat doneness preferences were measured using photographs that showed internal doneness and external brownness. We used a meat-derived HCA, B(*a*)P, and mutagen database with a questionnaire to estimate intake of PhIP, DiMeIQx, MeIQx, B(*a*)P, and mutagenic activity (revertants/g of daily meat intake). Data were analyzed with unconditional logistic regression.**
Results: **In analyses adjusted for age, sex, smoking, education, race, and diabetes, the odds ratio and 95% confidence interval for the highest compared with the lowest quintile were as follows: PhIP, 1.8 (1.0-3.1); DiMeIQx, 2.0 (1.2-3.5); MeIQx, 1.5 (0.9-2.7); B(*a*)P, 2.2 (1.2-4.0); and mutagenic activity, 2.4 (1.3-4.3).**
Conclusions: **HCAs and B(*a*)P from well-done barbecued and pan-fried meats may be associated with increased risk for pancreatic cancer.** (Cancer Epidemiol Biomarkers Prev 2005;14(9):2261–5)

Introduction

Pancreatic cancer is rapidly fatal in the majority of cases; there are no screening tests for early detection and about 90% of cases present with late stage disease (1, 2). The prognosis is generally dismal given that there are few therapeutic options. Identifying risk factors that can be modified is a potential means to reduce mortality from this cancer.

Numerous potential carcinogens are present in meat, including heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), and nitrosamines. The HCAs and PAHs are formed during the cooking of meats and the levels formed depend on cooking temperature and degree of doneness (3-6). Whereas baked and stewed meats do not contain these compounds, well-done barbecued and pan-fried meats typically contain high levels (7).

Several HCAs and at least one PAH have carcinogenic effects on the pancreas in experimental rodent models—although the most well-characterized models of experimental pancreatic carcinogenesis employ various nitrosamines or azaserine (8). The HCA, 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) produces benign tumors in rats (9), whereas the *N*-hydroxy heterocyclic arylamine, 4-hydroxyaminoquinoline 1-oxide induces both benign (10) and malignant (11) pancreatic tumors in rats. Two other HCAs, 3-amino-1,4-dimethyl-5*H*-pyriod[4,3-*b*]indole (Trp-P-1) and 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeQx), have shown tumor-promoting activity in hamsters (12). The PAH, dimethylbenzanthracene, when implanted in rats, induces pancreatic ductal adenocarcinomas that are histologically similar to those seen in humans (13, 14).

To investigate the role of HCAs and PAHs as possible human pancreatic carcinogens, we conducted a population-based case-control study. In a previous report from this study, we found that total meat consumption and red meat consumption were higher in cases than in controls, but these measures were not statistically significant predictors of risk (15). Positive associations were observed for well-done meat intake and fried meat intake and a strong and robust association was observed with grilled/barbecued red meat intake. Grilled/barbecued red meat consumption was associated with a nonlinear increased risk; the 90th relative to the 10th percentile of intake was associated with an odds ratio of 1.8 [95% confidence intervals (CI), 1.4-2.4]. To explore the underlying cause for this association, we have examined the estimated excess risk of pancreatic cancer associated with dietary intake of HCAs and the PAH, benzo(*a*)pyrene [B(*a*)P]. In addition, we have measured the association between pancreatic cancer and a mutagenic activity index based on daily meat intake—a measure that integrates all classes of mutagens.

Patients and Methods

Study Design. The Institutional Review Boards of the University of Minnesota, Minneapolis, the Mayo Clinic, and the U.S. Food and Drug Administration (National Center for Toxicological Research) approved this study protocol. A population-based case-control study of cancer of the exocrine

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Table 1. Characteristics of pancreatic cancer cases and controls

Variable, mean value (SD) or n (%)*	Cases (n = 193)	Controls (n = 674)
Age (y)	65.4 (11.6)	66.0 (12.5)
Sex		
Male	118 (61.1%)	380 (56.4%)
Female	75 (38.9%)	294 (43.6%)
Race		
Whites	181 (93.8%)	662 (98.2%)
African-American	8 (4.2%)	5 (0.7%)
Other	4 (2.1%)	7 (1.0%)
Cigarette smoking		
Never smoker	69 (35.8%)	16 (48.9%)
Past smoker	90 (46.6%)	281 (41.7%)
Current smoker	33 (17.2%)	77 (11.4%)
Smoking (pack-years)	21.6 (24.5)	18.0 (27.2)
Diabetes mellitus		
No	147 (76.2%)	622 (92.3%)
Yes	46 (23.8%)	52 (7.7%)
Education		
Less than high school graduate	32 (16.6%)	85 (12.6%)
High school graduate	69 (35.8%)	175 (26.0%)
Post high school education	91 (47.1%)	414 (61.4%)
Alcohol (servings/wk)	3.1 (6.3)	4.6 (8.4)
Total energy (kcal/d)	2,053 (820)	2,076 (811)
Dietary fat intake		
Animal (g/d)	38.4 (19.4)	37.7 (23.0)
Vegetable (g/d)	32.8 (17.6)	32.7 (18.8)
Fruit intake (servings/wk)	20.7 (19.3)	20.4 (13.6)
Vegetable intake (servings/wk)	18.5 (12.3)	22.1 (14.5)
Fruit and vegetable intake (servings/wk)	39.3 (27.0)	42.4 (24.0)

*Percentages may not add to 100 where information is missing.

pancreas was conducted using incident cases diagnosed between 1994 and 1998. For cases included in this analysis, the mean and median number of days between diagnosis and first contact for the study were 34 and 13 days, respectively. The study has been previously described in detail (15, 16). Briefly, controls were frequency-matched by age, and sex of the cases. In-person interviews were conducted with all subjects to obtain information including basic demographic information, complete cigarette smoking history, dietary intake, and medical and family history.

HCA and B(*a*)P Content. The subjects completed a semiquantitative food frequency questionnaire similar to the Willett food frequency questionnaire (17). Reported frequencies of consumption were used to estimate usual intake of fruits, cruciferous vegetables, fish, white meat, red meat, processed meat, coffee, tea, and alcohol. A detailed meat-cooking module was also completed. For meats prepared with variable cooking techniques, we obtained information on the typical level of doneness and cooking method as previously detailed by Sinha et al. (5).

The food composition database used to assign HCA and B(*a*)P content values to meat items on the study questionnaire were derived from previous analyses of meat samples as described (5). Briefly, HCA content (PhIP, DiMeIQx, and MeIQ) and B(*a*)P were determined in meat samples cooked by various methods to different degrees of doneness by the method of Gross and Gruter (18) using a solid-phase extraction/high-pressure liquid chromatography method. The mutagenic activity of sample extracts were measured using the standard plate incorporation assay with *Salmonella typhimurium* strain TA98. (6, 19). Agents with mutagenic activity in this assay that are believed to be most relevant to cooked meat include a variety of HCAs and B(*a*)P (6, 7, 18-22). We estimated intake of HCAs and mutagenic activity using responses from the food frequency questionnaire and the database that we developed for the HCA compounds and mutagenic activity in meat. First, by using frequency and portion size, we estimated gram consumption of each meat item (steak, hamburger patty, pork chops, bacon, etc.) by cooking technique (fried, grilled/barbecued, oven-broiled), and doneness level (by photographs). Then we derived intake of total HCA, B(*a*)P, and mutagenic activity (revertants/grams of daily meat intake) by multiplying grams of meat by concentration measured for each cooking technique/doneness level contribution for that meat type (4-6, 23, 24).

Statistical Methods. Odds ratios and 95% CIs were estimated by unconditional logistic regression. The dietary carcinogen variables were modeled both as a continuous variable for the test of trend, and by comparing the second, third, fourth and fifth quintiles to the first quintile. The likelihood ratio test was used to test for both linear and quadratic trends, comparing models without the carcinogen, with only a linear term, and with both a linear and quadratic term for the carcinogen. Quintiles were determined from the distribution among control subjects. All odds ratios were adjusted for age, sex, race, education, cigarette smoking (pack-years), and pack-years squared, and a history of diabetes for >2 years prior to the date of cancer diagnosis in cases or pseudo-diagnosis in controls. P values for trend were calculated using median values within each quintile.

Results

Cases and controls in this analysis were restricted to those who completed the meat module: 193 cases and 674 controls. The study population was 97% Caucasian (Table 1). The mean ages of the cases and controls were 65.4 and 66.0 years, respectively. Sixty-one percent of the cases and 56.4% of the controls were males. More cases than controls reported current or past cigarette smoking. Compared with never smokers these were associated with elevated odds ratios of 2.0 (95% CI, 1.2-3.3) and 1.5 (95% CI, 1.0-2.1), respectively. Cases were more likely than controls to report a history of diabetes (24% versus 8%) corresponding to a crude odds ratio of 1.9 (1.2-3.0) associated with pancreatic cancer.

Cases, when compared with controls, had higher mean levels of all the carcinogens—PhIP, DiMeIQX, MeIQX, and B(*a*)P as well as total mutagenic activity (Table 2). These measures are correlated and Spearman correlation coefficients between intake of the various dietary carcinogen measures (and the mutagenicity index) were calculated (Table 3). The coefficients between mutagenic activity index, PhIP, MeIQx, DiMeIQx, and B(*a*)P ranged between 0.43 and 0.92.

In multivariate-adjusted regression analyses, intakes of the HCAs, BAP, and total mutagenic activity were each associated with a nonlinear increased risk of pancreatic cancer. Increasing intake of each carcinogen and the mutagenic index across quintiles was associated with increased risk (Table 4). The highest odds ratios were seen in the highest quintiles of intake and, with the exception of MeIQX, these were all statistically significant. Additional adjustment for consumption of total

Table 2. Carcinogen intake and mutagenic activity index in pancreatic cancer cases and controls

Variable	Cases, mean (SD), median	Controls, mean (SD), median
PhIP (ng/d)	94.6 (117.8), 63.3	69.1 (106.1), 39.8
MeIQx (ng/d)	54.8 (54.7), 38	42.1 (50.3), 26.4
DiMeIQx (ng/d)	4.3 (5.0), 2.5	3.1 (4.2), 1.8
B(*a*)P (ng/d)	26.3 (50.3), 3.6	16.3 (33.7), 1.8
Mutagenic activity [revertant colonies/meat (g/d)]	6,618.4 (6,349.6), 4,625.6	4,921.9 (5,756.3), 3,289.6

Table 3. Spearman correlation coefficients for HCAs, B(*a*)P, and mutagenic activity

	PhIP (ng/d)	MeIQx (ng/d)	DiMeIQx (ng/d)	B(*a*)P (ng/d)	Mutagenic activity*
PhIP (ng/d)	1.00	0.63	0.60	0.72	0.80
MeIQx (ng/d)		1.00	0.89	0.50	0.92
DiMeIQx (ng/d)			1.00	0.43	0.84
B(*a*)P (ng/d)				1.00	0.64
Mutagenic activity*					1.00

NOTE: Based on 867 subjects.
*Mutagenic activity (revertant colonies / grams of meat / d).

calories, fat, fruits and vegetables, fiber, and alcohol generally increased the point estimates in each quintile, but decreased the precision of the estimates, and as the findings were not substantively altered, these variables were not included in final models.

Discussion

In this population-based case-control study, pancreatic cancer was positively associated with increased dietary intake of HCAs, PhIP, DiMeIQX, MeIQX, and the PAH, B(*a*)P. Risk estimates also increased with a mutagenic activity index, a biologically relevant and integrated measure of mutagenicity. The associations were robust to multivariate adjustment. We conclude that meat-derived HCAs and B(*a*)P—from well-done grilled and fried meat intake—are possible risk factors for pancreatic cancer.

In our previous study (15), we found that mean levels of total meat and red meat consumption were higher in cases than controls, but neither were strong or statistically significant predictors of risk in this study population. Grilled/barbecued red meat intake was a statistically significant predictor of pancreatic cancer risk. Fried red meat intake also increased risk, but was not statistically significant.

Few previous studies of pancreatic cancer have considered methods of meat preparation in their analyses and we are not aware of other studies that have incorporated doneness preferences, or estimates of carcinogenic and mutagenic dose to the extent we have here. Positive associations have been reported for fried and grilled meat (25), as well as fried and or grilled foods (26, 27); whereas null results have been reported for fried meat among smokers (28).

Other epidemiologic studies have analyzed the association of pancreatic cancer with meat and fat intake (which are closely correlated in the diet). Positive associations have been reported for the following: daily meat consumption (29); total meat, liver, ham, and sausages (30); red meat and salted/smoked meat (31); beef and bacon (32); pork and beef (33, 34); pork and fish, but not beef (35); beef, chicken, and pork (36), and fat (37-39). Null, inverse, and inconsistent associations have also been reported (40-47).

If pancreatic cancer risk is associated with the carcinogens formed during meat preparation and not meat intake per se, inconsistencies between different study populations are not surprising. Populations and individuals vary greatly in meat-cooking practices and doneness preferences. Although grilling and frying could produce high levels of carcinogens such as HCAs and PAHs, baking, stewing or broiling form only negligible levels (5). Failure to consider cooking techniques and doneness preferences, in addition to meat consumption, may result in misclassification of the relevant carcinogens and masking of true associations (48).

B(*a*)P and the HCAs considered here are reasonable candidates for human pancreatic carcinogens (49), and they

Table 4. Odds ratios associated with carcinogen intake and mutagenic activity and pancreatic cancer

	Quintile of daily dietary intake*				
	1	2	3	4	5
PhIP (ng/d)					
Median	0	17.3	39.4	72.9	175.3
Range	0-6.4	6.4-27.2	27.2-54.9	54.9-105.8	105.8-1,363.6
Cases	29	26	36	44	57
Odds ratio †	1.0 (ref)	0.9	0.7-2.1	1.4	1.8
95% CI, P_{trend} = 0.006		0.5-1.6		8.8-2.4	1.0-3.1
MeIQx (ng/d)					
Median	3.8	13.6	27.1	47.7	101.8
Range	0-8.8	8.8-19.7	19.7-36.7	36.7-64.4	64.4-580.2
Cases	29	30	34	44	55
Odds ratio	1.0 (ref)	1.0	1.1	1.4	1.5
95% CI, P_{trend} = 0.062		0.5-1.8	0.6-2.0	0.8-2.5	0.9-2.7
DiMeIQx (ng/d)					
Median	0	0.8	1.9	3.4	7.5
Range	0-0.4	0.4-1.3	1.3-2.6	2.6-4.8	4.8-52.2
Cases	25	36	35	38	58
Odds ratio	1.0 (ref)	1.6	1.4	1.5	2.0
95% CI, P_{trend} = 0.029		0.9-2.8	0.8-2.5	0.8-2.7	1.2-3.5
B(*a*)P (ng/d)					
Median	0.3	0.8	1.8	10.4	53.7
Range	0-0.5	0.5-1.1	1.1-3.1	3.1-25.9	26.0-305.1
Cases	22	35	35	48	52
Odds ratio	1.0 (ref)	1.6	1.4	2.0	2.2
95% CI, P_{trend} = 0.050		0.9-2.8	0.8-2.6	1.1-3.7	1.2-4.0
Mutagenic activity ‡					
Median	419	1,652	3,290	5,771	11,045
Range	0-1,079	1,080-2,309	2,310-4,329	4,330-7,334	7,335-53,026
Cases	24	31	38	36	63
Odds ratio	1.0 (ref)	1.3	1.5	1.4	2.4
95% CI, P_{trend} = 0.003		0.7-2.5	0.9-2.7	0.8-2.5	1.3-4.3

*Quintiles were determined using the control data.
† Adjusted for age, sex, smoking (pack-years and pack-years squared), education, race, and diabetes.
‡Mutagenic activity (revertant colonies / grams of meat / d).

represent a substantial portion of meat-derived mutagens/carcinogens in their respective classes (7, 22). In rodent models, PhIP, the most mass-abundant of theses HCAs, forms high levels of DNA adducts in the pancreas (50), and is preferentially taken up by pancreatic acini (51). Of note, however, there are other known carcinogenic HCA and PAH mutagens in cooked meat (48, 21) that may contribute to pancreatic carcinogenesis. In addition, there are components of meat, such as fat and iron, that may be relevant to carcinogenesis in the pancreas as well (3, 49).

A strength of this study is that it was designed to address the hypothesis that dietary HCAs and B(*a*)P intake are associated with risk of pancreatic cancer. We collected detailed information, from direct interviews, on cooking practices and doneness levels for specific types of commonly consumed meats. This is essential to most accurately estimate the carcinogen intake and mutagenicity index associated with meat intake. Estimates of dietary carcinogen intakes, like other dietary nutrient intakes, are imperfect. The HCAs and PAHs in cooked meat are correlated with each other and with other potentially carcinogenic constituents. There is variation in both the absolute and relative levels of these carcinogens in any meal— and diet—, that cannot be precisely captured by a survey instrument (3-7). It is difficult therefore, to implicate specific meat-derived carcinogens and cancer risk in population studies (52).

Because approximately half of all pancreatic cancer cases die within 3 months of diagnoses, case-control studies of this disease are particularly challenging, and thus our conclusions carry caveats. In this, as in other studies of pancreatic cancer, the proportion of all eligible cases enrolled was low (~30%), thus creating the potential for selection bias.

In addition, pancreatic cases that do enroll are usually quite ill, and as a result, may report their food intake history differently than do controls. However, it is hard to imagine why selection bias or reporting bias would result in over-reporting by cases of meat preparation methods—particularly grilling, frying and well-done meat preferences that would result in the higher estimates of dietary HCAs and B(*a*)P.

Our evidence lends support to the view that HCAs and B(*a*)P, formed during the cooking of meat, are human carcinogens. These hypotheses should be replicated, ideally in a prospective study.

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